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RESEARCH ARTICLE

Skin sympathetic nerve activity as a biomarker for outcomes in spontaneous intracerebral hemorrhage

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Abstract

Objective: A rapid and accurate forecast for the early prognosis of ICH patients is challenging. This study investigated whether heart rate variability (HRV) and skin sympathetic nerve activity (SKNA) could prognosticate poor neurological outcomes in ICH patients. **Methods**: Between November 2020 and November 2021, we studied 92 spontaneous ICH patients in the First Affiliated Hospital of Nanjing Medical University. Glasgow Outcome Scale (GOS) score at 2 weeks after the ICH was used to categorize patients into good and poor outcome groups. The modified Rankin Scale (mRS) assessed patients' ability to live independently for 1 year. We utilized a portable high-frequency electrocardiogram (ECG) recording system to record the HRV and SKNA information in ICH patients and control participants. **Results**: 77 patients were eligible for the prediction of neurological outcome and were allocated into the good (n = 22) or poor (n = 55) outcome groups based on the GOS grade. In univariate logistic regression analysis, significant variables that could differentiate the outcomes were age, hypertension, tracheal intubation, Glasgow Coma Scale (GCS) score, existing intraventricular hemorrhage, white blood cells, neutrophil, lnVLF, lnTP, and aSKNA. Variables in the best fit multivariable logistic regression model were age, hypertension, GCS score, neutrophils, and aSKNA. The GCS score was the only independent risk factor for poor outcomes. At 30 days and 1 year of follow-up, patients with lower aSKNA had poor outcomes. **Interpretation**: ICH patients had reduced aSKNA, which could be a prognostic indicator. A lower aSKNA suggested a worse prognosis. The present data indicate that ECG signals could be helpful for prognosticating ICH patients.

Introduction

Intracerebral hemorrhage (ICH) is a severe type of stroke that is the leading cause of disability and death. The short-term mortality rate is close to 50%.[1] Signs of the neurologic outcome are often delayed, so the accurate and early identification of patients' nervous system prognosis is beneficial to assist medical decision-making.

An electrocardiogram (ECG) contains information helpful to the diagnosis of cardiovascular diseases and produces signals that can reflect the autonomic nerve function of the body. Heart rate variability (HRV) obtained from ECG can be used as a noninvasive and simple method to evaluate autonomic nervous function. HRV has been used to assess disease prognosis in recent years.[2] ICH patients usually have reduced HRV, which can predict a poor outcome for acute ICH patients.[3–6]

At present, through specific filtering, the signal of the corresponding frequency isolated from the ECG signal can reflect the information on skin sympathetic nerve

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activity, which is consistent with stellate ganglion and thoracic sympathetic nerve activity.[7] Compared with HRV, SKNA can more directly reflect the influence of nervous system injury on the sympathetic nerve. SKNA has been used in many clinical settings, including monitoring atrial fibrillation,[8] detection of obstructive sleep apnoea,[9] and the effect of anesthetic and sedative agents on sympathetic activity.[10] However, no association of SKNA with clinical outcomes in ICH patients has been reported.

Here, we examined SKNA and HRV-related prognosticators that could reflect acute ICH. It was hypothesized that signals in the ECG could be predictors of the outcome for ICH patients.

Materials and Methods

The Ethics Committee of the First Affiliated Hospital of Nanjing Medical University approved this prospective and observational study. The clinical data of the patients were obtained through the electronic medical record system. All patients or their next of kin gave written informed consent.

Participants

We recruited acute ICH patients admitted to the intensive care unit (ICU) of the First Affiliated Hospital of Nanjing Medical University between November 2020 and November 2021. The inclusion criteria were patients over 18 years of age with spontaneous acute ICH. Exclusion criteria were patients with ischaemic stroke or hemorrhagic conversion, atrial fibrillation or other arrhythmias, and patients with hemodynamic instability or shock. Control participants were recruited from an outpatient department of cardiovascular medicine. They were gender and age-matched participants who had not experienced an acute cardiovascular or neurological event.

Study design

The electronic medical record system was used to obtain demographic data, medical history, laboratory examination results, imaging, and other clinical baseline data. Two weeks after spontaneous ICH, a favorable neurologic outcome was defined as a Glasgow Outcome Scale (GOS)[11] score of 4 (moderate disability) or 5 (good recovery), as determined by medical professionals. Patients whose GOS score ranged from 1 to 3 (1 = death, 2 = persistent vegetative state, 3 = severe disability) were considered to have a poor outcome. The ECG data were collected when the patients' conditions were stable. Glasgow Coma Scale (GCS) score was evaluated at the time of ECG signal acquisition. Each patient was followed for more than 1 year and follow-up data were collected through discharge summaries and telephone interviews with the patients and their referral hospitals. If the patient died during hospitalization or was automatically discharged due to giving up treatment, the time of death was considered as the endpoint of follow-up. If the patient was discharged with improvement, follow-up would be conducted at 30, 60 days, and 1 year to understand the patient's prognosis. All-cause death was analyzed on day 30. The modified Rankin Scale (mRS) was used to assess patients' ability to live independently for 1 year.

ECG data acquisition and analysis

The ECG data were collected using a portable high-frequency ECG acquisition device and stored on a memory card. The files are automatically named after the time. The device has a sampling rate of 4000 Hz, and our previous studies[12] have shown that it has the same effect as neu-ECG-based acquisition and analysis.[13] In short, 0.05–150 Hz was used as the frequency content of adult ECG, and the 500–1000 Hz bandpass filter was used to extract the SKNA signal (Fig. 1).

ECG data of the first 300 s after signal stabilization were used for analysis to prevent possible deviations in data selection. The *wqrs* algorithm extracted the RR interval of the ECG signal, and then the HRV was calculated and analyzed by a program downloaded from PhysioNet (https://physionet.org/physiotools/matlab/wfdb/wfdb-app-matlab/).[14] ECG data with poor signal quality were identified and flagged by the algorithm. In addition, all ECGs for HRV analysis were plotted and determined by an independent ECG physician. If atrial flutter, atrial fibrillation, or other arrhythmias occurred in the segment analyzed, the ECG data's HRV analysis was discarded. SKNA voltage and RR interval data were corrected by subtracting the upper and the lower 2.5th percentile data to avoid any possible effects of extreme noise on the analysis. The calculation of the average voltage of SKNA (aSKNA) is based on the previous method by using a customized MATLAB program.[13] The aSKNA was measured to reflect overall sympathetic nerve activity within 5 min, indirectly reflecting stellate ganglion activity.

The HRV time-domain analysis includes the standard deviation of all sinus RR intervals (SDNN), square root of the mean square of differences between adjacent normal-to-normal (NN) intervals (RMSSD), percentage of the number of pairs of adjacent NN intervals differing >50 ms in the total NN intervals (pNN50), acceleration capacity (AC), and deceleration capacity (DC). The frequency-domain analysis contains very-low-frequency

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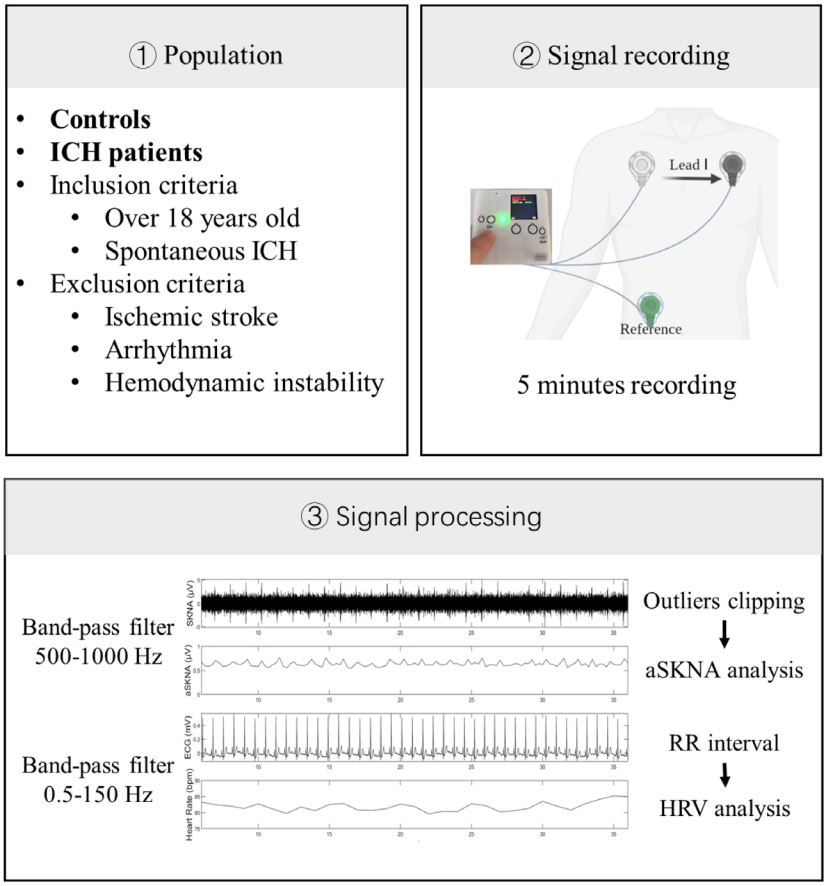

Figure 1. Graphical illustration for participants, signal recording, and signal processing in this study.

power (VLF), low-frequency power (LF), high-frequency power (HF), the ratio of low to high-frequency power (LF/HF), and the total power (TP). The LF and HF were also normalized by TP.[15] The geometric-domain index, including the triangular index and Poincaré plot, and complexity variables, including approximate entropy (ApEn) and sample entropy (SampEn), were also analyzed.

Statistical analysis

Patient demographic and clinical characteristics were compared between the two groups of ICH patients with different prognoses. ICH patients were also compared with age and gender-matched control participants. Univariate logistic regression analysis was used to evaluate the prediction of adverse outcomes by related variables. Variables in univariate logistic regression with $p < 0.05$ were put into the multivariate logistic regression model, and the results were expressed by odds ratios (ORs) and 95% confidence intervals (CIs).

R software (version 4.1.0) was used for all statistical analyses and data visualization. The "TableOne" package was used to process clinical baseline data. Continuous variables with a normal distribution are presented as the mean and standard deviation (SD), and nonnormal distributed variables are presented as the median and interquartile range (IQR). Classification variables are expressed as numbers or percentages. Student's *t*-test, Wilcoxon rank-sum test, and chi-square test were used to compare between groups. The "ROCit" package was used for receiver operating characteristic curve (ROC) analysis and the calculation of the area under the curve (AUC). The optimal truncation value of the predictors was calculated using the Youden index method. Univariate and multivariate logistic regression analyses were performed to evaluate the prediction of adverse outcomes by related variables. Bidirectional stepwise regression was used to screen variables according to the minimum AIC criterion. Kaplan–Meier analysis was performed between two groupings based on the optimal aSKNA cut-off value, and the log-rank test was used to compare the

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all-cause death. Significance was defined when two-sided $p < 0.05$.

Results

Patient characteristics

After applying the inclusion and exclusion criteria, 92 ICH patients were included, and the ECG data were analyzed according to established analytical procedures. Unfortunately, 15 low-quality or arrhythmia ECG datasets flagged by the algorithm were discarded after quality control. Thus, complete data from 77 patients were eligible for the prediction of the neurological outcome. Seventy-two age-, sex-, and hypertension-matched control participants were also recruited and underwent high-frequency ECG monitoring. ECG data from the control group were also quality-controlled.

Main results

The comparisons of HRV/aSKNA variables between the ICH patients and control participants are shown in Table 1. Both groups were predominantly male, 61.1% vs. 67.5%, for the ICH and control participants, respectively. ICH patients had a faster heart rate (86.70 ± 11.27 vs. 93.28 ± 17.77, $p = 0.008$). Compared to control participants, the SDNN and rMSSD of ICH patients were slightly decreased, but no significant differences were observed (SDNN: 25.93 vs. 29.15, $p = 0.304$; rMSSD: 22.68 vs. 25.24, $p = 0.322$) in the time-domain analysis. The pNN50 was slightly lower (0.02 vs. 0.03, $p = 0.044$). In the frequency-domain analysis, ICH patients had lower VLF, LF, and HF without TP correction (VLF: 130.86 vs. 341.28, $p = 0.003$; LF: 59.38 vs. 187.51, $p < 0.001$; HF: 81.34 vs. 190.58, $p < 0.001$). The TP of the ICH patients was reduced (365.10 vs. 860.57, $p = 0.001$). However, there was no significant difference between LF n.u. and HF n.u. after TP correction. No significant differences were found in other HRV indices of the nonlinear analysis between the two groups. Additionally, ICH patients had lower aSKNA (0.87 vs. 1.12, $p < 0.001$).

The GOS was performed 14 days after admission in ICH patients with satisfactory ECG data quality and it was classified as either a good outcome (GOS = 4–5, $n = 22$) or a poor outcome (GOS = 1–3, $n = 55$). Comparisons of baseline characteristics, HRV-related variables, and aSKNA scores between the two groups are shown in Table 2. There were significant differences in age ($p = 0.005$), hypertension ($p = 0.003$), tracheal intubation ($p = 0.001$), GCS score ($p < 0.001$), existing intraventricular hemorrhage ($p = 0.002$), white blood cells (WBCs) ($p = 0.035$), neutrophils ($p = 0.028$), VLF ($p = 0.015$), TP ($p = 0.025$), and aSKNA ($p = 0.020$) between the good and poor outcome groups. In the poor outcome group, the incidences of respiratory failure, heart failure, CHD, diabetes, and pneumonia were higher but the difference was not significant.

Table S1 displays the medication usage of patients, with a majority of patients utilizing antihypertensive agents (63.6%), antibiotics (87.0%), sedatives (54.5%), and analgesics (67.5%). However, the results indicate no significant differences in medication usage between the two groups. Table 3 shows the OR and 95% CI of related characteristics for poor outcomes by univariate and multivariate logistic regression analysis. In univariate logistic regression analysis, significant variables that could differentiate outcomes were age, hypertension, tracheal

Table 1. Comparison of HRV/aSKNA variables between ICH patients and control participants.

	Control ($n = 72$)	ICH ($n = 77$)	p-value
Male/female	44/28 (61.1/38.9)	52/25 (67.5/32.5)	0.518
Age, years	57.76 (8.74)	60.52 (16.38)	0.207
Hypertension	31 (43.1)	36 (46.8)	0.773
HR, bpm	86.70 (11.27)	93.28 (17.77)	0.008
SDNN, ms	29.15 (12.62)	25.93 (23.43)	0.304
rMSSD, ms	25.24 (10.68)	22.68 (19.29)	0.322
pNN50	0.03 [0.01, 0.06]	0.02 [0.00, 0.04]	0.044
VLF, ms^2	341.28 [174.72, 536.42]	130.86 [47.89, 419.76]	0.003
LF, ms^2	187.51 [86.36, 337.68]	59.38 [22.81, 268.99]	<0.001
LF, n.u.	35.69 [23.22, 46.16]	33.42 [18.54, 43.56]	0.314
HF, ms^2	190.58 [92.90, 323.26]	81.34 [39.98, 223.60]	<0.001
HF, n.u.	44.48 [29.17, 57.61]	44.23 [27.26, 60.15]	0.773
LF/HF	0.82 [0.50, 1.58]	0.67 [0.46, 1.35]	0.334
TP, ms^2	860.57 [472.74, 1277.81]	365.10 [150.27, 1103.29]	0.001
AC	−4.38 (2.11)	−4.17 (3.88)	0.678
DC	4.16 (1.97)	3.87 (3.44)	0.533
SD1, ms	17.87 (7.56)	16.06 (13.66)	0.322
SD2, ms	36.33 (17.94)	32.08 (31.14)	0.314
SD2/SD1	0.56 (0.27)	0.57 (0.29)	0.761
SampEn	1.35 (0.41)	1.44 (0.50)	0.233
ApEn	1.04 (0.22)	1.08 (0.26)	0.440
aSKNA, μV	1.12 (0.35)	0.87 (0.34)	<0.001

AC, acceleration capacity; ApEn, approximate entropy; aSKNA, average skin sympathetic nervous activity; DC, deceleration capacity; HF, high-frequency bands; HR, heart rate; LF, low-frequency bands; pNN50, Percentage of successive RR intervals that differ by more than 50 ms; rMSSD, Root mean square of successive RR interval differences; SampEn, sample entropy; SD1 and SD2, standard deviations of short and long axis of Poincaré plot; SDNN, Standard deviation of NN intervals; TP, total power; VLF, very-low-frequency bands.

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Table 2. Comparison of patient characteristics and HRV/aSKNA variables between poor and good outcomes.

	Overall n = 77	Poor outcome (GOS = 1–3), n = 55	Good outcome (GOS = 4, 5), n = 22	p-value
Male/female	52/25 (67.5/32.5)	39/16 (70.9/29.1)	13/9 (59.1/40.9)	0.465
Age, years	60.52 (16.38)	63.78 (14.31)	52.36 (18.62)	0.005
Respiratory Failure	12 (15.6)	11 (20.0)	1 (4.5)	0.180
Heart Failure	7 (9.1)	7 (12.7)	0 (0.0)	0.188
Hypertension	36 (53.2/46.8)	32 (58.2)	4 (18.2)	0.003
CHD	2 (2.6)	2 (3.6)	0 (0.0)	0.910
Diabetes	5 (6.5)	5 (9.1)	0 (0.0)	0.342
Pneumonia	61 (79.2)	46 (83.6)	15 (68.2)	0.230
Tracheal	38 (49.4)	34 (61.8)	4 (18.2)	0.001
Hospital stays, day	20.06 (13.54)	20.69 (14.36)	18.50 (11.39)	0.525
GCS	9.53 (4.65)	8.07 (4.32)	13.18 (3.28)	<0.001
Subatentorial	8 (10.4)	6 (10.9)	2 (9.1)	1
Intoventricles	34 (44.2)	31 (56.4)	3 (13.6)	0.002
PCT, ng/mL	0.28 [0.11, 0.75]	0.28 [0.13, 0.83]	0.26 [0.11, 0.50]	0.718
WBC	12.08 (5.63)	12.93 (6.16)	9.94 (3.27)	0.035
Lymphocyte	0.86 (0.43)	0.83 (0.46)	0.93 (0.32)	0.389
Monocyte	0.81 (0.55)	0.85 (0.62)	0.70 (0.25)	0.278
Neutrophil	10.30 (5.15)	11.11 (5.58)	8.27 (3.15)	0.028
Eosinophil	0.09 (0.23)	0.11 (0.27)	0.06 (0.08)	0.447
Basophil	0.03 (0.03)	0.03 (0.03)	0.02 (0.02)	0.173
HCT, %	33.31 (7.04)	33.56 (6.95)	32.66 (7.37)	0.615
K^+, mmol/L	4.00 (0.67)	4.09 (0.74)	3.78 (0.42)	0.068
Na^+, mmol/L	142.99 (6.55)	143.35 (6.80)	142.08 (5.95)	0.445
Urea, mmol/L	11.23 (12.30)	11.69 (7.77)	10.11 (19.74)	0.614
ALT, pg/mL	48.99 (55.82)	49.05 (56.23)	48.85 (56.09)	0.989
AST, pg/mL	43.65 (26.35)	43.04 (20.64)	45.16 (37.60)	0.752
Albumin, g/L	39.42 (7.84)	39.71 (8.40)	38.70 (6.33)	0.614
HR, bpm	93.28 (17.77)	94.36 (18.44)	90.59 (16.08)	0.404
SDNN, ms	25.93 (23.43)	24.03 (24.22)	30.69 (21.08)	0.263
rMSSD, ms	22.68 (19.29)	21.64 (18.97)	25.29 (20.26)	0.457
pNN50, %	0.02 [0.00, 0.04]	0.02 [0.00, 0.04]	0.02 [0.00, 0.10]	0.295
VLF, ms^2	130.86 [47.89, 419.76]	84.34 [33.57, 372.87]	259.96 [193.56, 668.59]	0.015
LF, ms^2	59.38 [22.81, 268.99]	49.75 [19.97, 121.71]	104.17 [26.32, 361.55]	0.169
LF, n.u.	33.42 [18.54, 43.56]	33.42 [17.80, 44.51]	33.39 [21.75, 42.96]	0.839
HF, ms^2	81.34 [39.98, 223.60]	76.44 [39.72, 184.93]	99.21 [43.84, 381.36]	0.361
HF, n.u.	44.23 [27.26, 60.15]	44.68 [29.41, 61.41]	38.56 [22.47, 57.96]	0.172
LF/HF	0.67 [0.46, 1.35]	0.66 [0.46, 1.21]	0.90 [0.53, 1.78]	0.234
TP, ms^2	365.10 [150.27, 1103.29]	284.85 [119.39, 698.35]	842.78 [300.67, 1474.57]	0.025
AC	−4.17 (3.88)	−3.83 (3.58)	−5.03 (4.53)	0.221
DC	3.87 (3.44)	3.57 (3.14)	4.61 (4.07)	0.234
SD1, ms	16.06 (13.66)	15.32 (13.43)	17.90 (14.35)	0.457
SD2, ms	32.08 (31.14)	29.45 (32.36)	38.66 (27.47)	0.244
SD2/SD1	0.57 (0.29)	0.60 (0.30)	0.50 (0.25)	0.146
SampEn	1.44 (0.50)	1.48 (0.53)	1.33 (0.44)	0.247
ApEn	1.08 (0.26)	1.09 (0.26)	1.04 (0.27)	0.507
aSKNA, μV	0.87 (0.34)	0.82 (0.30)	1.01 (0.40)	0.020

AC, acceleration capacity; ALT, alanine aminotransferase; ApEn, approximate entropy; aSKNA, average skin sympathetic nervous activity; AST, aspartate transaminase; CHD, coronary heart disease; DC, deceleration capacity; GCS, glasgow coma scale; HCT, hematocrit; HF, high-frequency bands; HR, heart rate; LF, low-frequency bands; PCT, preprocalciton; pNN50, Percentage of successive RR intervals that differ by more than 50 ms; rMSSD, Root mean square of successive RR interval differences; SampEn, sample entropy; SD1 and SD2, standard deviations of short and long axis of Poincaré plot; SDNN, Standard deviation of NN intervals; TP, total power; VLF, very-low-frequency bands; WBC, white blood cell.

intubation, GCS score, existing intraventricular hemorrhage, WBC, neutrophil count, lnVLF, lnTP, and aSKNA. Variables in the best fit multivariable logistic regression model were Age, Hypertension, GCS score, neutrophil, and aSKNA. The GCS score (p = 0.002) was the only significant independent risk factor for a poor outcome.

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Table 3. Univariate and multivariate logistic regression analyses of HRV-related variables for prediction of poor outcome.

	β	Std. error	OR	95% CI	*Z*-value	*p*-value
Univariate logistic regression analysis						
Age	−0.047	0.018	0.954	(0.922–0.988)	−2.626	0.009
Hypertension	−1.834	0.617	0.160	(0.048–0.535)	−2.975	0.003
Tracheal	−1.986	0.619	0.137	(0.041–0.461)	−3.211	0.001
GCS	0.301	0.077	1.351	(1.161–1.573)	3.889	0.000
Intoventricles	−2.102	0.678	0.122	(0.032–0.462)	−3.099	0.002
WBC	−0.166	0.078	0.847	(0.727–0.986)	−2.139	0.033
Neutrophil	−0.174	0.080	0.840	(0.718–0.983)	−2.176	0.030
ln VLF	0.330	0.158	1.391	(1.021–1.897)	2.089	0.037
ln TP	0.386	0.185	1.470	(1.024–2.111)	2.089	0.037
aSKNA	1.648	0.769	5.195	(1.151–23.452)	2.143	0.032
Multivariate logistic regression analysis, minAIC = 62.414						
Age	−0.052	0.027	0.949	(0.901–1.001)	−1.907	0.056
Hypertension	−1.57	0.811	0.208	(0.042–1.02)	−1.935	0.053
GCS	0.3	0.096	1.35	(1.12–1.629)	3.14	0.002
Intoventricles	−1.159	0.827	0.314	(0.062–1.588)	−1.401	0.161
NE	−0.153	0.096	0.858	(0.711–1.036)	−1.596	0.111
aSKNA	1.773	1.14	5.888	(0.631–55.01)	1.556	0.120

aSKNA, average skin sympathetic nervous activity; GCS, glasgow coma scale; TP, total power; VLF, very-low-frequency bands; WBC, white blood cell.

Figure S1 shows the ROC curve and AUC for the 10 statistically significant variables in univariate logistic regression. The GCS score had the largest value of AUC value (0.809). Figure 2 shows the ROC curve for the 6 variables in multivariate logistic regression. The AUC of the combined model made up of 6 variables was 0.923. Patients were divided into two groups for survival analysis based on the optimal cut-off value (0.6725) of aSKNA (Fig. 3A). Over the entire period of 30 days of follow-up, 12 (15.6%) patients died, and there were no lost patients. In the Kaplan–Meier analysis, patients whose aSKNA values were lower than 0.6725 had a poor outcome, and the difference between the two groups was already significant on the 14th day (p = 0.006), and became even more apparent on the 30th day (p = 0.00044). Figure 3B illustrates the mRS scores of patients at the one-year mark, with 56.0% and 28.8% of patients in each respective group having experienced mortality (mRS = 6). Patients with aSKNA value greater than 0.6725 had a better functional prognosis (mRS <3), with proportions of 38.5% and 12.0% in the two groups, respectively (p = 0.035).

Discussion

This study has several important findings: (1) Some frequency-domain indicators of HRV and SKNA activity were reduced in patients with spontaneous ICH compared with control participants. (2) In addition to conventional

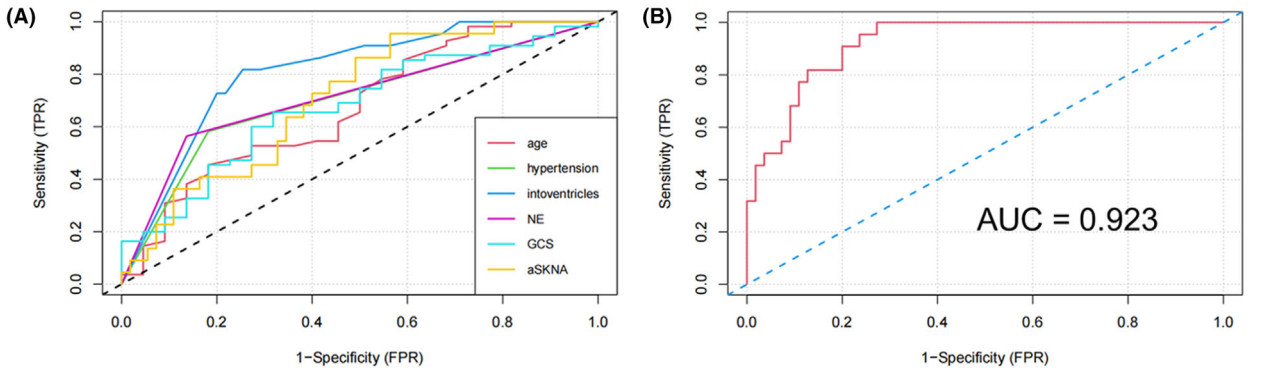

Figure 2. ROC curve for the 6 variables in multivariate logistic regression (A). ROC curve and AUC for the combined model made up of 6 variables in multivariate logistic regression (B).

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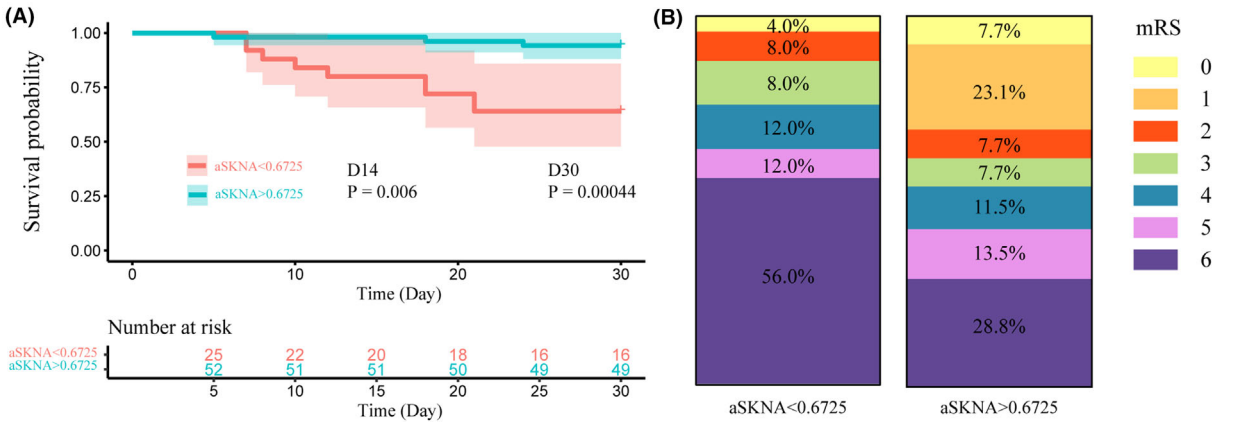

Figure 3. (A) Survival analysis of patients grouped based on the optimal cut-off value (aSKNA = 0.6725) during 30 days follow-up. (log-rank test, $p = 0.00044$). (B) Comparison of mRS between ICH two groups at 1 year according to the cut-off value of aSKNA.

predictors, VLF, TP, and aSKNA could indicate the prognosis of ICH patients. (3) Other predictors combined with aSKNA could enhance the prediction of a poor neurologic outcome in spontaneous ICH patients.

Both the sympathetic and parasympathetic nerves modulate cardiac rhythm. There is a complex interaction between the nervous and cardiovascular systems.[16] There is now substantial evidence that higher brain function (cortical), brainstem, and autonomic nerves influence cardiac electrophysiology and arrhythmias and that these may act as interactive systems.[17] After acute intracerebral hemorrhage, the regulation of the brain-cardiac axis is very complex. It has been reported that 70%–85% of patients with acute intracerebral hemorrhage had abnormal ECGs.[18] Its mechanism may be that the acute hemorrhage of the brain damages the brain tissue and produces cerebral edema, leading to an increase in intracranial pressure, which may affect the regulation of the heart due to the compression of the temporal lobe sulcus or the cardiovascular center of the medulla oblongata. When it directly or indirectly involves the thalamic autonomic center, it can lead to nervous system disorders and cause various arrhythmias and cytopathic cardiac changes (including acute myocardial damage, myocardial ischemia, and heart failure). The sympathetic nerves are widely distributed in the brain's blood vessels and they play a vital role in improving the cerebral circulation and promoting brain metabolism. Their axon ends mainly release norepinephrine, which regulates vascular contraction and expansion. Autonomic nervous disorder after ICH usually manifests as an inhibition of sympathetic activity.[19] The mechanism may be that sympathetic activity is inhibited, and the abnormal release of norepinephrine when the patient's condition with ICH is stable, leading to cerebral vasodilation and preventing cerebral vasospasm. In addition, complex mechanisms include catecholamine release, immune response, and inflammation.[17] With the continuous improvement of electrophysiological techniques, it has been reported that SKNA and HRV can reflect the activity of sympathetic and parasympathetic nerves,[20] but there is hardly any research on SKNA and HRV in ICH patients.

The indices of HRV can reflect the complex balance of the autonomic nerve. There have been excellent reviews of the significance of various HRV indicators.[2,15] Briefly, some of the markers in HRV represent sympathetic and parasympathetic activity, respectively. However, this is not entirely clear because the sympathetic and parasympathetic nerves are mutually modulated to create the overall state of autonomic nervous function. Our results showed that the frequency-domain indices of ICH patients, such as LF, HF, and TP, were lower than those of controls (Table 1). LF and HF represent the relative activity of sympathetic and parasympathetic nerves, respectively.[15] However, the standardized values of LF n.u. and HF n.u. after TP correction were not significantly different between the two groups. Thus, although frequency-domain analysis of HRV can provide potential insights into the body's complex autonomic nervous function, sometimes the differences could be confusing. For example, in one study, VLF, LF, and HF were higher in the control group than in the heart failure group.[21] In many other studies, frequency domain indicators have shown similar results between the two groups in the patient cohort.[4,22–25]

SKNA is well related to ganglion nerve activity (SGNA).[7] And SKNA varies with changes in the source of stress, and readings of SKNA increase significantly in classic sympathetic nerve activation experiments such as cold water pressor testing (CPT) and Valsalva maneuver,

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making it evident that can represent sympathetic activity.[26] However, SKNA not only serves as a good response indicator for comparing acute sympathetic activation experiments, but the absolute value of its readings also reflects the patient's current sympathetic excitation state and provides predictions for disease prognosis. SKNA has been used to predict diseases or certain functions, such as obstructive sleep apnoea,[9] recurrent syncope,[27] acute myocardial infarction,[28] haemodialysis,[20] fitness,[29] etc.

Clinically available tools used to determine neurologic prognosis include coma scales, multiple medical imaging, electroencephalogram (EEG), and somatosensory evoked potential. These methods are not very convenient, and sometimes the results are obtained with a lag. And although biomarkers of poor prognosis have been described for ICH, they have not been used for the proactive management of patients and were instead utilized solely for prognostic prediction. The use of SKNA may change this paradigm. The recording method of SKNA is the same as that of ECGs. As a routine vital sign monitoring method, SKNA has the characteristics of great convenience and real-time information updates. And SKNA is devoid of parasympathetic components, allowing for a more intuitive understanding of a patient's physiologic status by clinicians. For example, if an ICH patient's SKNA reading is markedly elevated or decreased, adjustment of sedative dosing may be warranted. Although there is a long way from bench to bedside, the potential of SKNA in ICH management is promising.

In our study, the result of ICH injury was the downregulation of sympathetic nerve activity, which indicated the lack of response of the patient's autonomic nervous system to external stimuli. This suggests that ICH patients with more severe conditions may have insufficient sympathetic nerve responsiveness. A study by Issa Kutkut et al. on patients with cardiac arrest undergoing targeted temperature management (TTM) also showed similar results.[30]

The patients whose aSKNA was lower than the optimal cut-off value had a lower survival probability at the 30-days follow-up and worse functional prognosis (mRS <3) at 1 year. In addition, although GCS was the only significant independent factor for evaluating the prognosis in the multivariable model, the combined model robustly improved the prediction performance (AUC = 0.923). It was demonstrated that SKNA is a sensitive, quantitative method to detect sympathetic function and it has significant application value in evaluating the prognosis of patients with ICH.

Several limitations might affect the findings of this project. First, we excluded some data that influenced the HRV analysis. Although the occurrence of arrhythmia events did not affect the SKNA analysis, we still discarded the data to ensure good data integrity and matching, which might lead to bias. Second, for ethical and data stability reasons, all ECG data were collected after the ICH patients had passed the acute phase, so the patient's disease period was relatively obscure. Third, the use of antihypertensive, β-blocker, sedative, and analgesic drugs may affect the patient's autonomic nervous system and consequently, the readings of HRV/SKNA during measurement. While there was no difference in medication usage between the two groups of patients analyzed.

Conclusions

The present results indicate that aSKNA and some HRV indices can be helpful for early prognostication of neurologic outcomes in spontaneous ICH patients. Signals in the ECG are useful for diagnosing cardiovascular diseases and contain beneficial information about the nervous system.

Author Contributions

Weiwei Wang and Hongyi Cheng are the joint first authors who contributed equally to methodology, statistics analysis, writing, and visualization; Zhiqiao Lin, Yantao Xing, Xiaoyuan Zhong, and Xichen Liang contributed to data curation and methodology; Yike Zhang and Chang Cui contributed in the data processing. Yan Chen, Quan Cao, and Minglong Chen are the joint corresponding authors solely responsible for this work; they contributed to conceptualization, funding acquisition, and review and editing.

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Conflict of Interest Statement

The authors declare that they have no competing interests.

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Data Availability Statement

The datasets generated during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was set in compliance with Helsinki Declaration and was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2015-SRFA-085). Non-opposition to participate in the study from the patient or his/her next of kin was collected prior to inclusion.

Consent for Publication

Not applicable.

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Supporting Information

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Figure S1.
Table S1.
Figure S1 Captions.

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